UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

08 CV 6286

SANOFI-AVENTIS,
SANOFI-AVENTIS U.S. LLC, AND
BRISTOL-MYERS SQUIBB SANOFI
PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs,

v.

SUN PHARMACEUTICAL INDUSTRIES, LTD. AND
SUN PHARMA GLOBAL, INC.,

Defendants.

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Sanofi-Aventis, Sanofi-Aventis U.S. LLC, and the Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership, for their Complaint herein against defendants Sun Pharmaceutical Industries, Ltd., and Sun Pharma Global, Inc., hereby allege as follows:

NATURE OF ACTION

1. This is an action for patent infringement.

PARTIES

2. Plaintiff, Sanofi-Aventis is a corporation organized and existing under the laws of France, having its principal place of business at 174 Avenue de France, Paris, France. Sanofi-Aventis is a global healthcare company, whose core therapeutic areas are cardiovascular disease and thrombosis, diseases of the central nervous system, cancer, and internal medicine.

3. Plaintiff, Sanofi-Aventis U.S. LLC is the U.S. subsidiary of Sanofi-Aventis, and is a limited liability company formed under the laws of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807.

4. Plaintiff, the Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership ("the Partnership"), a partnership between Bristol-Myers Squibb and Sanofi-Aventis, is registered in the state of Delaware, and having a mailing address at P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543. The Partnership is responsible for the marketing and sale of Plavix® in the United States and numerous countries in North America, South America, Central America, and elsewhere.

5. On information and belief, defendant, Sun Pharmaceutical Industries, Ltd. is an Indian Corporation with a principal place of business in Mumbai, India.

6. On information and belief, defendant, Sun Pharma Global Inc. is a company incorporated and existing under the laws of the British Virgin Islands and having a place of business in Dubai, United Arab Emirates. On information and belief, Sun Pharma Global Inc. is a wholly owned subsidiary of Sun Pharmaceutical Industries, Ltd.

7. On information and belief, the acts of Sun Pharma Global Inc. complained of herein, were done at the direction of, with the authorization of, and with the cooperation, participation, and assistance of Sun Pharmaceutical Industries, Ltd., and/or its subsidiaries.

8. Sun Pharmaceutical Industries, Ltd., and Sun Pharma Global Inc., are referred to hereinafter, collectively as "Sun."

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

10. On information and belief, Sun is subject to personal jurisdiction in this district because Sun maintains continuous and systematic contacts with the United States, including the State of New York, and because it has committed the acts of patent infringement alleged herein within the United States. On information and belief, Sun, directly or through its subsidiaries and affiliates, markets and sells generic drugs throughout the United States, including the State of New York. On information and belief, Sun has submitted to the United States Food and Drug Administration (the "FDA") an abbreviated new drug application ("ANDA") under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of clopidogrel bisulfate tablets, which has been assigned ANDA 90-494.

11. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b), (c), and (d), and 28 U.S.C. § 1400(b).

CLAIM FOR RELIEF - PATENT INFRINGEMENT

12. Sanofi-Aventis holds approved new drug application ("NDA") 20-839 for Plavix®, the active ingredient in which is clopidogrel bisulfate. Plavix® was approved by the FDA on November 17, 1997, and is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented

by recent stroke, recent myocardial infarction, or established peripheral arterial disease, and in patients with acute coronary syndrome.

13. Clopidogrel can be referred to by several chemical names, which refer to the same chemical structure. The chemical name referred to in Sanofi-Aventis' NDA is methyl (+)-(S)-alpha-(2-Chlorophenyl)-6,7-dihydrothieno(3,2-c)pyridine-5(4H)-acetate. The chemical names referred to in several Sanofi-Aventis patents are the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate, and (4)-(S)-alpha-(O-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5-acetate. Clopidogrel bisulfate is the hydrogen sulfate salt of clopidogrel.

14. Sanofi-Aventis is the owner of United States Patent No. 4,847,265 ("the '265 Patent") (attached as Exhibit A), which discloses and claims, among other things clopidogrel, clopidogrel bisulfate, other salts of clopidogrel, and pharmaceutical compositions containing those compounds. The '265 Patent was duly and legally issued on July 11, 1989. The '265 Patent is exclusively licensed to the Partnership.

15. Sanofi-Aventis is the owner of United States Patent No. 6,429,210 ("the '210 Patent") (attached as Exhibit B), which discloses and claims, among other things, a novel polymorphic form of clopidogrel bisulfate, known as Form 2 and pharmaceutical compositions containing Form 2 clopidogrel bisulfate. The '210 Patent was duly and legally issued on August 6, 2002. The '210 Patent is exclusively licensed to the Partnership.

16. On information and belief, Sun has submitted to the FDA an ANDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial

manufacture, use, and sale of clopidogrel bisulfate tablets, which has been assigned ANDA 90-494.

17. On information and belief, Sun's ANDA includes the use of Form 2 of clopidogrel bisulfate.

COUNT 1
INFRINGEMENT OF U.S. PATENT NO. 4,847,265

18. Plaintiffs repeat and reallege paragraphs 1-17 above as if fully set forth herein.

19. On information and belief, Sun submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its clopidogrel bisulfate formulation before the expiration of the '265 Patent.

20. By filing the ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its proposed drug products before the expiration of the '265 Patent, Sun has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic clopidogrel bisulfate products for which Sun seeks approval in its ANDA will also infringe one or more claims of the '265 Patent.

21. On information and belief, Sun made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, that the '265 Patent is invalid, unenforceable and/or not infringed by its proposed ANDA product.

22. On information and belief, Sun's ANDA seeks approval to manufacture, use and sell pharmaceutical formulations containing clopidogrel bisulfate, which is the precise compound described and claimed in the '265 Patent.

COUNT 2
INFRINGEMENT OF U.S. PATENT NO. 6,429,210

23. Plaintiffs repeat and reallege paragraphs 1 - 22 as if fully set forth herein.

24. On information and belief, Sun submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its Form 2 clopidogrel bisulfate formulation before the expiration of the '210 Patent.

25. By filing the ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its proposed drug products before the expiration of the '210 Patent, Sun has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic clopidogrel bisulfate products for which Sun seeks approval in its ANDA will also infringe one or more claims of the '210 Patent.

26. On information and belief, Sun made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '210 Patent is invalid.

27. On information and belief, Sun's ANDA seeks approval to manufacture, use and sell the Form 2 polymorph of clopidogrel bisulfate, which is the precise compound described and claimed in the '210 Patent.

28. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Sun's generic clopidogrel bisulfate products be a date which is not earlier than the expiration dates of the '265 and '210 Patents and any further exclusivity to which Plaintiffs are or become entitled.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. Judgment that Sun has infringed one or more claims of the '265 and '210 Patents by filing the aforesaid ANDA relating to Sun's generic clopidogrel bisulfate products;

B. A permanent injunction restraining and enjoining Sun and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of generic clopidogrel bisulfate products as claimed in the '265 and '210 Patents;

C. An order that the effective date of any approval of the aforementioned ANDA relating to Sun's generic clopidogrel bisulfate product be a date which is not earlier than the expiration dates of the '265 and '210 Patents and any further exclusivity to which Plaintiffs are or become entitled;

D. Monetary relief to the extent that Sun has committed or does commit any act outside the scope of 35 U.S.C. § 271(e)(1);

E. A reasonable attorney fee based on the exceptional nature of this case;

F. The costs and disbursements of this action; and

G. Such other and further relief as the Court may deem just and proper.

Dated: July 11, 2008

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Exhibit A

United States Patent [19]
Badorc et al.

[11] **Patent Number:** **4,847,265**
[45] **Date of Patent:** **Jul. 11, 1989**

[54] **DEXTRO-ROTATORY ENANTIOMER OF METHYL ALPHA-5 (4,5,6,7-TETRAHYDRO (3,2-C) THIENO PYRIDYL) (2-CHLOROPHENYL)-ACETATE AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

[75] Inventors: **Alain Badorc**, Roquettes; **Daniel Fréhel**, Toulouse, both of France

[73] Assignee: **Sanofi**, France

[21] Appl. No.: **155,550**

[22] Filed: **Feb. 12, 1988**

[30] **Foreign Application Priority Data**

Feb. 17, 1987 [FR] France 87 02025
Nov. 27, 1987 [FR] France 87 16516

[51] **Int. Cl.**[4] **A61K 31/44**; C07D 495/04
[52] **U.S. Cl.** **514/301**; 546/114
[58] **Field of Search** 546/114; 514/301

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,529,596 7/1985 Aubert et al. 546/115

FOREIGN PATENT DOCUMENTS

0099802 7/1983 European Pat. Off. .

OTHER PUBLICATIONS

Fieser et al., Advanced Org. Chem.-Reinhold Publishing Co., N.Y., (1961), pp. 85-88.

Primary Examiner—Mary C. Lee
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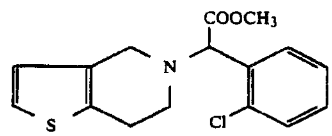
[57] **ABSTRACT**

The present invention relates to the dextro-rotatory enantiomer of Formula



and its pharmaceutically acceptable salts with platelet aggregation inhibiting activity.

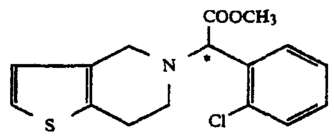
The invention also relates to a process for the preparation of this compound starting from the racemate and the pharmaceutical compositions containing it.

7 Claims, No Drawings

DEXTRO-ROTATORY ENANTIOMER OF METHYL ALPHA-5 (4,5,6,7-TETRAHYDRO (3,2-C) THIENO PYRIDYL) (2-CHLOROPHENYL)-ACETATE AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING IT

The present invention relates to the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate, a process for its preparation and pharmaceutical compositions containing it.

The compound of the invention corresponds to the following formula (I):



(I)

in which the C* is an asymmetric carbon atom. In fact, this formula represents both the dextro-rotatory molecule claimed as well as its levo-rotatory enantiomer. The racemic mixture corresponding to this formula was described in the French patent application published under the No. 2 530 247. Hereafter the dextro-rotatory enantiomer claimed according to the invention will be designated by I_d and the levo-rotatory enantiomer by I_l.

It is known that the optical rotatory power of a compound depends on the solvent in which it is measured and on its concentration in this solvent. The optical rotatory power of the dextro-rotatory isomer according to the invention is positive in methanolic solution.

In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers.

The invention also relates to the addition salts of the compounds of formula (I_d) with pharmaceutically acceptable mineral or organic acids.

The compound (I_d) is an oil whereas its hydrochloride exists as a white powder. The oily products are usually difficult to purify and it is preferable to use for the preparation of pharmaceutical compositions crystalline products which can usually be purified by recrystallization.

However, it has been observed in the present case that some of the salts of compound (I_d) usually precipitate in an amorphous form and/or that they are hygroscopic, a property which makes them difficult to handle on an industrial scale. Thus, the salts of carboxylic acid and sulfonic acids classically used in pharmacy have been prepared, acids such as acetic, benzoic, fumaric, maleic, citric, tartaric, gentisic, methane-sulfonic, ethanesulfonic, benzenesulfonic and laurylsulfonic acids as well as the salts of dobesilic acid (m.p.=70° C.) and para-toluenesulfonic acid (m.p.=51° C.), the purification of which proved to be difficult.

Among the mineral and organic acid salts of the dextro-rotatory isomer of the compound of Formula (I_d) salts have been found which crystallize easily, are not hygroscopic and are sufficiently water-soluble as to make their use as active medicinal principles particularly advantageous.

The present invention thus relates more particularly to the hydrogen sulfate, the taurocholate and the hydrobromide of the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

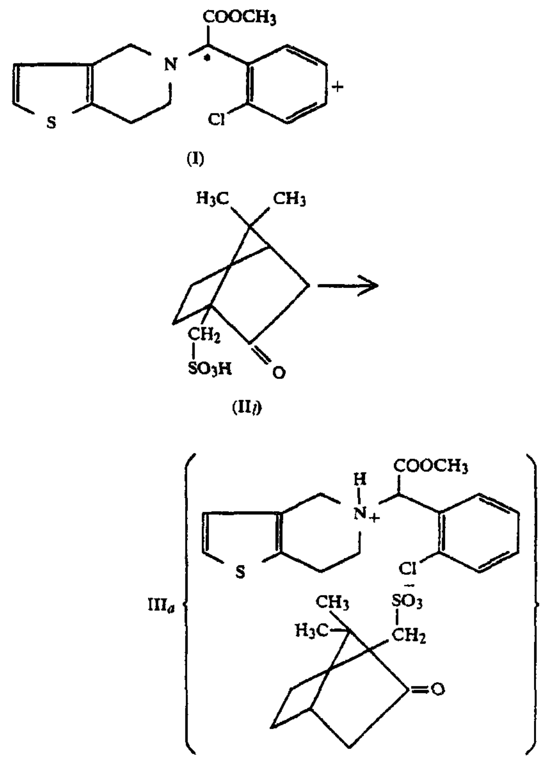
These salts are prepared in a standard manner by the action of the corresponding acid on the base in solution in a solvent from which they precipitate spontaneously or after addition of a non-solvent of the salt.

The dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate can be prepared by forming the salt of the racemic compound with an optically active acid in a solvent, repeated recrystallizations of the salt until a product of constant optical rotatory power is obtained, followed by the liberation of the dextro-rotatory isomer from its salts by a base; if required, a salt is formed between the dextro-rotatory isomer and a pharmaceutically acceptable acid.

The optically active acid may advantageously be levo-rotatory camphor-10-sulfonic acid.

One and the same solvent may be used for salt formation and recrystallization: acetone is ideally suited in this case.

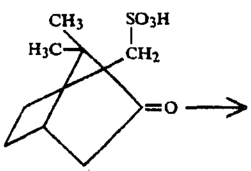
The chiral, levo-rotatory camphor-10-sulfonic acid of Formula (II_l) is allowed to react in an inert solvent with the racemic mixture of Formula (I) according to the following reaction scheme:



Salt formation may be carried out in solvents such as alcohols, ketones, dimethylformamide. The salt precipitates spontaneously or is isolated by salting out or evaporation of the solvent. A mixture of two diastereoisomers of Formula (IIIa) is formed. By repeated recrystallizations from a solvent such as acetone the precipitate

is enriched in the salt of the dextro-rotatory isomer of compound (I). After each recrystallization the optical rotatory power $[\alpha]_D^{20}$ of the precipitate is measured at 20° C. in methanol at a concentration varying between 1.5 and 2 g/100 ml. When the $[\alpha]_D^{20}$ stops increasing the base of Formula (I_D) is liberated from the salt (IIIa) by the action of a base such as sodium or potassium hydrogen carbonate in aqueous media at temperatures varying between 5° C. and 20° C. Evaporation of the filtrate of the first recrystallization IV after the crystals of the precipitated salt (IIIa) have been filtered off, gives a mixture enriched in the salt of (I_1) enantiomer. The basification of this mixture of diastereoisomeric salts with a weak base such as sodium or potassium hydrogen carbonate in aqueous solution at temperatures varying between 5° C. and 20° C. leads to a mixture of the two enantiomers (I_d) plus (I_1) enriched in the levo-rotatory enantiomer (I_1).

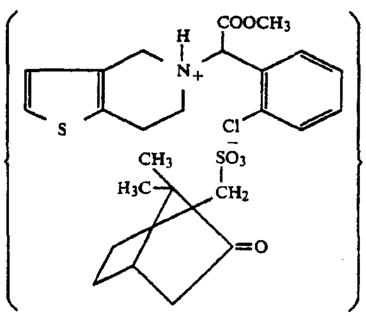
This mixture (I_d)+(I_1) enriched in enantiomer (I_1) is allowed to react with dextro-rotatory camphor-10-sulfonic acid which will be designated as (II_d) in a solvent according to the following reaction scheme:



(I_d) + (I_l)
(I_l) > (I_d)
with (I_l)
in excess

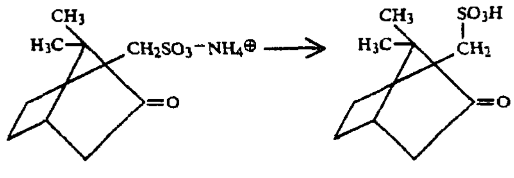
(II_d)
(II) dextro-rotatory)

IIIb



The crystalline mixture of diastereoisomeric salts (IIIb) obtained is recrystallized from acetone until the optical rotatory power $[\alpha]_D^{20}$ of the precipitate remains constant. As previously mentioned the optical rotatory power $[\alpha]_D^{20}$ of the diastereoisomeric salt (IIIb) is determined after each recrystallization.

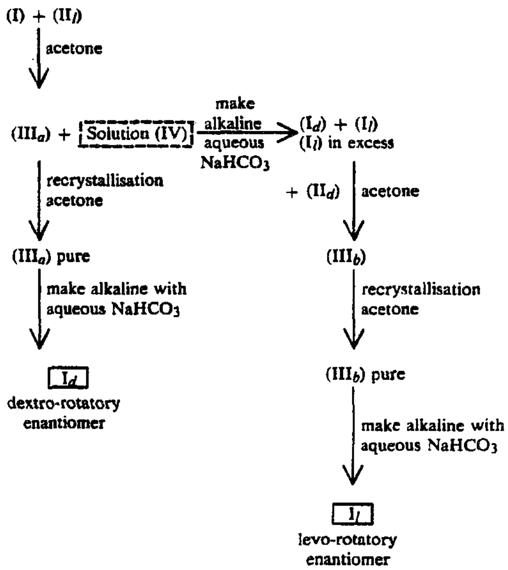
The liberation of the stereoisomeric (I_1) from its salt is carried out in a standard manner, like that for compound (I_d). Levo-rotatory comphor-10-sulfonic acid (II_1) may be obtained from commercially available ammonium camphor-10-sulfonate of Formula (V) according to the reaction scheme:



(V) (II_l)

An aqueous solution of the ammonium salt (V) is chromatographed on an Amberlite IRN-77 resin. After lyophilization of the eluate camphor-10-sulfonic acid of Formula (II_1) is recovered.

The entire sequence of the process is shown schematically below:



Each of the pure enantiomers (I_d) and (I_1) may be converted into a salt by means of the standard methods: for example, the hydrochlorides are prepared by the addition of a solution of hydrogen chloride gas in diethyl ether to a solution of (I_d) or (I_1) in diethyl ether.

DETERMINATION OF THE ENANTIOMERIC PURITY OF THE DEXTRO-ROTATORY (I_d) AND LEVO-ROTATORY (I_1) ENANTIOMERS

Two methods have been used:

proton NMR spectroscopy with the addition of a chiral rare earth

high pressure liquid chromatography using a chiral stationary phase.

(a) Proton NMR spectroscopy with the addition of a chiral rare earth The enantiomeric purity (optical purity) was determined by ^1H 60 MHz NMR spectroscopy in the presence of a rare earth chiral complex according to the method described by G. M. WHITESIDES et al. (J. Am. Chem. Soc. 1974, 96, 1038).

In the racemic product (I), the hydrogen attached to the asymmetric centre in the α position to the ester function appears as a singlet (chemical shift δ=4.87 ppm in $CDCl_3$ as solvent. The addition of the rare earth complex Eu(tfc)$_3$ [tris 3-(trifluoromethyl hydroxyme-

thylene)-d-camphorato europium (III)] to the probe containing a solution of the racemate (I) in $CDCl_3$ leads to the resolution of the initial singlet into two, well-separated singlets corresponding to the proton of each of the two enantiomers (I_d) and (I_l). When the molar ratio of rare earth complex/compound (I)=0.4, the separation between the two singlets is about 6 Hz.

With each of the two enantiomers prepared, (I_d) and (I_l), the same procedure was used as for the racemate (I). The smaller chemical shift corresponds to the proton of the dextro-rotatory enantiomer (I_d) and the larger chemical shift to the levo-rotatory enantiomer (I_l).

The precision of the method was determined by comparing the ^1H (60 MHz) NMR spectra obtained with and without addition of the rare earth complex for each of the two enantiomers (I_d) and (I_l) in the pure state or as mixtures containing increasing quantities of one of the enantiomers. It was observed that it was possible to detect easily more than 5% by weight of one enantiomer in the presence of the other.

(b) High pressure liquid chromatography using a chiral stationary phase The study was conducted with a liquid chromatograph HP-1084 using a UV detector at 215 nm. The chiral stationary phase was DEAE silica (10 microns) onto which was grafted alpha-1 acid glycoprotein (0.4×100 mm) (ENANTIOPAC R-LKB). The mobile phase consisted of an aqueous phosphate buffer mixture 8 mM (NaH_2PO_4/Na_2HPO_4) containing 0.1M of NaCl, adjusted to pH=7.4, and 15% of isopropanol (v/v). The flow rate was fixed at 0.3 ml/minute and the temperature of the column was maintained at 18°-20° C. Under these conditions, the dextro-rotatory enantiomer (I_d) has a retention time of 45 minutes and the levo-rotatory enantiomer (I_l) has a retention time of 35 minutes.

The precision of the determination of the optical purity of the two enantiomers was estimated by chromatographing each of the two enantiomers (I_d) and (I_l) prepared either alone or as a mixture containing increasing amounts of one of the enantiomers. It was observed that it was easy to detect:

2% (weight/weight) of enantiomer (I_d) in enantiomer (I_l)

4% (weight/weight) of enantiomer (I_l) in enantiomer (I_d).

Under these conditions it may be concluded that the optical purity of the two enantiomers (I_d) and (I_l) obtained according to the examples is at least equal to 96% for the dextro-rotatory enantiomer (I_d) and at least equal to 98% for the levo-rotatory enantiomer (I_l).

The following examples are non-restrictive and are presented to illustrate the present invention.

EXAMPLE 1

Salts of dextro-rotary methyl-alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

(a) levo-rotatory camphor-10-sulfonic acid

A column of Amberlite IRN-77 resin is prepared and tested by passing 1N hydrochloric acid through it and then by washing this column of acidified resin abundantly with water. Levo-rotatory ammonium camphor-10-sulfonate is dissolved in a minimum of water and applied to the column of resin previously prepared. Elution is carried out with water. The eluted fractions containing the acid are lyophilized.

White crystals, m.p.=198° C.; $[\alpha]_D^{20}=-20.53$ (c=2.075 g/100 ml water).

(b) Camphor-10-sulfonic acid salt of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990 B).

32 g (0.0994 mole) of racemic methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate are dissolved in 150 ml of acetone. 9.95 g (0.0397 mole) of levo-rotat camphor-10-sulfonic acid monohydrate are added. The clear solution is left to stand at room temperature. After 48 hours some crystals have formed. The reaction mixture is concentrated to 50 ml and left to stand at room temperature for 24 hours. The crystals obtained are filtered off, washed with acetone and dried (yield: 55% on the basis of the starting racemate).

White crystals, m.p.=165° C., $[\alpha]_D^{20}=+24.67$ (c=1.58 g/100 ml; methanol).

The crystals obtained above are redissolved in the minimum of boiling acetone (50 ml). The crystals obtained after cooling are filtered off, washed with acetone and dried (yield: 88%).

White crystals, m.p.=165° C., $[\alpha]_D^{20}=+24.75$ (c=1.68 g/100 ml; methanol).

(c) Dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

12 g (0.022 mole) of the pure product obtained in (b) are dissolved in a minimum of water. After cooling to 5° C., the aqueous solution obtained is made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic extracts are dried over anhydrous sodium sulfate. On evaporation of the solvent a colorless oil is obtained (quantitative yield). Oil, $[\alpha]_D^{20}=+51.52$ (c=1.61 g/100 ml; methanol).

(d) The hydrochloride of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (dextro-rotatory) (SR 25990 A).

7 g (0.0228 mole) of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate are dissolved in 100 ml of diethyl ether. 30 ml of a solution of 1N HCl in diethyl ether are added and the crystals obtained are filtered off. The crystals are washed with diethyl ether and dried (yield: 94%).

White crystals, m.p.=117° C., $[\alpha]_D^{20}=+62.23$ (c=1.82 g/100 ml; methanol).

(e) The hydrogen sulfate of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990 C).

800 ml of a saturated aqueous solution of sodium bicarbonate are added to a suspension of 200 g of SR 25990 B in 800 ml of dichloromethane. After vigorous shaking, the organic phase is separated, dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is dissolved in 500 ml of ice-cold acetone and 20.7 ml of concentrated sulfuric acid (93.64%, d=1.83) are added drop-wise. The precipitate formed is isolated by filtration and washed with 1,000 ml of acetone, then dried in a vacuum oven at 50° C.

139 grams of analytically pure white crystals are thus obtained with a melting point of 184° C. Empirical formula: $C_{16}H_{16}ClNO_2S.H_2SO_4$ $[\alpha]_D^{20}=+55.10$ (c=1.891 g/100 ml; methanol).

(f) The hydrobromide of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990D).

150 ml of an aqueous solution of sodium bicarbonate are added to a suspension of 20 g of SR 25990 B in 200

ml of dichloromethane. The residue obtained after separation of the organic phase, drying and evaporation of the solvent is dissolved in 150 ml of diethyl or diisopropyl ether, and 4.4 ml of a 48% (wt/v) aqueous solution of hydrobromic acid are added drop-wise. The precipitate formed is isolated. After drying, 14.4 g of crystals are obtained with a melting point of 111° C. (yield 99%).

13.4 g of these crystals are recrystallized from a mixture of isopropyl ether (100 ml) and isopropanol (150 ml) to give 10.2 g of analytically pure hydrobromide: m.p.=140° C.; empirical formula: $C_{16}H_{16}ClNO_2S.HBr$ $[\alpha]_D^{20}=+59.23$ (c=2.09 g/100 ml; methanol).

(g) The taurocholate of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990E).

The sodium salt of taurocholic acid is chromatographed on Amberlite IRN-77 resin by eluting with water. The fractions obtained are lyophilized.

3 g (0.0054 mole) of SR 25990B are treated with a saturated aqueous solution of sodium bicarbonate and the mixture is extracted with dichloromethane. The organic phase is separated, dried over sodium sulfate and evaporated to dryness. The free base obtained is taken up in 30 ml of isopropanol; 2.8 g (0.0054 mole) of taurocholic acid dissolved in 100 ml of isopropanol are added to this solution. The mixture is stirred overnight at room temperature, then evaporated to dryness. The residue solidifed on being triturated with ether. 3.5 g of beige crystals are obtained. m.p.=120° C. $[\alpha]_D^{20}+=39.53$ (c=1.791 g/100 ml of methanol). $C_{16}H_{16}ClNO_2S.C_{26}H_{45}NO_7S$; C, H, N analyses in agreement with theory.

EXAMPLE 2

Salts of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

(a) Salt of d-camphor-10-sulfonic acid (SR 25989 B)

After separation of SR 25990 B in Example 1-b the solvent is evaporated from the acetone filtrate obtained.

The residue is taken up in water and diethyl ether. The ethereal phase is decanted. The aqueous phase is cooled to 5° C. and made alkaline with a saturated aqueous solution of sodium bicarbonate. The aqueous alkaline phase is extracted with diethyl ether. The ethereal extracts are pooled and dried over anhydrous sodium sulfate.

On evaporation of the solvent an oil is obtained which is purified by filtration through a bed of silica (eluant: diethyl ether). A colourless oil is recovered consisting of a mixture of about 65% of the levo-rotatory enantiomer and 35% of the dextro-rotatory enantiomer, proportions determined by means of ^1H (60 MHz) NMR spectroscopy after the addition of chiral, rare earth complex.

16.66 g (0.0517 mole) of the mixture thus obtained are dissolved in 70 ml of acetone. 7.77 g (0.0310 mole) of dextro-rotatory camphor-10-sulfonic acid monohydrate are added. The homogeneous mixture is left to stand overnight at room temperature. The crystals obtained are filtered off, washed with acetone and dried (yield: 44% based on the mixture).

The crystals obtained are dissolved in a minimum of refluxing acetone (60 ml). The precipitate obtained on cooling to room temperature is filtered off, washed with acetone and dried. White crystals, m.p.=167° C., $[\alpha]_D^{20}=-24.85$ (c=1.79 g/100 ml; methanol).

(b) Levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

11.3 g (0.0204 mole) of the camphor-10-sulfonate obtained in (a) are dissolved in a minimum of water. The aqueous solution obtained is cooled to 5° C. and made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic solution is dried and the solvent is evaporated. A colourless oil is isolated (quantitative yield).

Oil $[\alpha]_D^{20}=-50.74$ (c=1.58 g/100 ml; methanol).

(c) The hydrochloride of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25989 A).

Prepared according to the method described in Example 1(d). Yield: 94%.

White crystals, m.p.=117° C., $[\alpha]_D^{20}=-62.56$ (c=1.80 g/100 ml; methanol).

(d) The hydrogen sulfate of levo-rotatory methyl-alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25989 C).

70 g (0.126 mole) of the camphor sulfonate SR 25989 B obtained are treated as described in (a) above with a saturated aqueous solution of sodium bicarbonate in the presence of dichloromethane. The organic phase is separated, dried over sodium sulfate and evaporated to dryness. The residue is taken up in 300 ml of acetone and 7.2 ml (0.126 mole) of concentrated sulfuric acid are added drop-wise. After being stirred the crystals formed are filtered off and washed with acetone. 47.8 g of white crystals are obtained. m.p.=182° C. $[\alpha]_D^{20}=-51.61$ (c=2.044 g/100 ml; methanol). The analysis (C,H,N) are in agreement with theory.

PHARMACOLOGICAL STUDY

The platelet aggregation inhibiting activity and the toxicity of these new compounds were compared to those of the racemic mixture described in the French Pat. No. 82.12599 (Publication No. 2 530 247).

A description will now be given of the results of this study which demonstrates another advantage of the invention, namely that the salts of the dextro-rotatory isomer have a better therapeutic index than the salt of the racemic mixture; in fact, the levo-rotatory isomer exhibits almost no platelet aggregation inhibiting activity and its toxicity is markedly higher than that of its dextro-rotatory homologue.

The platelet aggregation inhibiting activities and the antithrombotic activities of the compounds were studied in the rat by standard methods.

The activity on the aggregation of plates induced by ADP or collagen was determined ex-vivo.

The products dissolved in ethanol (200 mg/ml) and diluted in water containing gum arabic (5%-wt/v) were administered by the oral route to groups of five female rats of the CD-COBS strain, weighing 250–300 g, in amounts of 10 ml of suspension per kilogram two hours before blood samples were taken.

The blood samples were taken from animals anesthetized with diethyl ether by puncture of the abdominal aorta and placed over a 3.8% aqueous solution of sodium citrate (1 vol/9 volumes of blood). The platelet-rich plasma was then isolated by centrifugation at 200 g for 10 minutes.

Aggregation is induced by the addition of 2 μl of aggregating solution to 400 μl of platelet-rich plasma.

The aggregating solutions used were: a 500 μM aqueous solution of ADP marketed by Boehringer Mannheim (final concentration 2.5 μM), and a solution of collagen marketed by Sigma (type 1) at a concentration of 0.25 g/100 ml in 3% acetic acid (v/v) (final concentration 12.5 μg/ml).

The aggregation of the platelets was monitored as described in the method by G. V. R. Born in Nature 194, p. 927 (1967) using a Coultronics® aggregometer at a temperature of 37° C. and agitation of 900 rpm.

For aggregation with ADP, the aggregometer generates a curve representing a platelet aggregation as measured by a change in optical density. The height of this curve is defined as the height of aggregation. The percentage of aggregation is the relation between the aggregation height measured and the height corresponding to 100% aggregation × 100. The percentage of inhibition is determined by the relation:

$$\frac{\text{Control aggregation height} - \text{produced aggregation height}}{\text{Control aggregation height}} \times 100$$

The results obtained for the aggregation with ADP for the hydrochloride of the racemic mixture (PCR 4099), the hydrogen sulfates of the dextro-rotatory (SR 25990 C) and levo-rotatory (SR 25989 C) isomers on the one hand, and for PCR 4099 and the hydrochlorides of the dextro-rotatory (SR 25990 A) and levo-rotatory (SR 25989 A) on the other, are shown in Table I; they demonstrate that the levo-rotatory isomer is inactive and that the dextro-rotatory isomer is at least as active as the racemate.

TABLE I

PRODUCT	DOSE mg/Kg P.O	QUANTITY of base administered	% AGGREGATION	% INHIBITION	P**
Controls			42.4 +/− 1.5		
PCR 4099	4.48	3.84	29.8 +/− 2.4	30	0.01
(racemate)	8.97	7.69	17.2 +/− 2.2	59	0.001
	17.9	15.38	11.1 +/− 2.3	74	0.001
SR 25989C	20	15.38	41.0 +/− 1.5	3	n.s
	40	30.76	37.1 +/− 1.7	13	n.s
SR 25990C	1.25	0.96	39.4 +/− 1.3	7	n.s
	2.5	1.92	28.4 +/− 2.3	33	0.01
	5	3.84	14.0 +/− 1.6	67	0.001
	10	7.69	8.5 +/− 1.6	80	0.001
Controls			33.8 +/− 2.3		
SR 25990E	10	3.84	9.6 +/− 3	72	0.001
	20	7.69	4 +/− 1.6	88	0.001
			AGGREGATION HEIGHT		
Controls			103 +/− 5		
PCR 4099	2.5	2.14	86 +/− 5	17	0.05
(racemate)	5	4.28	72 +/− 8	30	0.05
	12.5	10.71	32 +/− 9	69	0.001
SR 25989A	25	22.46	101 +/− 1	2	n.s
SR 25990A	2.5	2.25	67 +/− 7	35	0.01
	5	4.49	26 +/− 5	75	0.001
	12.5	11.23	19 +/− 4	82	0.001
	25	22.46	11 +/− 1	89	0.001

*mean of results +/− standard error of the mean (SEM)
**Student test
***aggregation height in mm: mean +/− SEM (n = 5)
n.s. not significant

For the aggregation with collagen, the percentage of inhibition is the difference of the slopes of the curves representing the variation of the optical density as a function of time for the control and the product to be tested divided by the slope of the control multiplied by 100. The results shown in Table II demonstrate again that only the dextro-rotatory isomer is active whereas the salts have comparable activities.

TABLE II

PRODUCT	DOSE mg/Kg P.O	QUANTITY of base administered	SLOPE	% INHIBITION	P**
Controls			4.8 +/− 0.3		
PCR 4099	4.48	3.84	3.6 +/− 0.2	25	0.05
(racemate)	8.97	7.69	2.7 +/− 0.3	44	0.01
	17.9	15.38	1.5 +/− 0.3	69	0.001
SR 25989C	20	15.38	4.3 +/− 0.2	10	n.s
	40	30.76	4.0 +/− 0.2	17	n.s
SR 25990C	1.25	0.96	4.5 +/− 0.3	6	n.s
	2.5	1.92	4.1 +/− 0.2	15	n.s
	5	3.84	2.3 +/− 0.1	52	0.001
	10	7.69	1.7 +/− 0.3	65	0.001
Controls			3.5 +/− 0.1		
SR 25990E	10	3.84	2.1 +/− 0.5	40	0.05
	20	7.69	1.4 +/− 0.4	60	0.01
Controls			3.97 +/− 0.29		
PCR 4099	2.5	2.14	3.13 +/− 0.33	21	n.s
(racemate)	5	4.28	2.94 +/− 0.34	26	0.05
	12.5	10.71	2.19 +/− 0.42	45	0.01
SR 25989A	25	22.46	4.32 +/− 0.29	10	n.s
SR 25990A	2.5	2.25	3.05 +/− 0.19	23	0.05
	5	4.49	1.24 +/− 0.22	69	0.001
	12.5	11.23	0.86 +/− 0.14	78	0.001
	25	22.46	0.74 +/− 0.13	81	0.001

**Student test
n.s. not significant

The antithrombotic activity of these compounds has also been studied in the test of venous thrombosis on a screw thread described by Kumada T. et al. in Thromb. Res 18 p. 189 (1980).

Female rats of the same type as those previously described, in groups of 10 animals, were anesthetized with diethyl ether and their vena cava was isolated after abdominal incision.

A metallic screw thread 21 mm long consisting of a dentist's drill, marketed by Dyna (France) size No. 30, was introduced into the lumen of this vein just below the renal bifurcation descending towards the iliac veins, without damaging the wall; 19 to 20 mm of the length of the screw thread are implanted and the remaining 1 mm protrudes through the closed stomach into the exterior.

The thrombi formed rapidly and five hours later, under pentobarbital anesthesia, the abdomen is re-opened and ligatures are placed above and below the screw thread which is withdrawn after longitudinal incision of the vein and the isolated thrombus is weighed.

The results which are presented in Table III show that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer and the racemate.

TABLE III

PRODUCT	DOSE mg/Kg P.O admin.	QUANTITY of base	WEIGHT of thrombi*	VARIATION %	P**
Controls			3.9 +/− 0.3		
PCR 4099	4.48	3.84	2.17 +/− 0.24	44	0.001
(racemate)	8.97	7.69	1.39 +/− 0.15	64	0.001
	17.9	15.38	1.00 +/− 0.19	74	0.001
SR 25989C	40	30.76	4.17 +/− 0.42	−7	n.s
SR 25990C	1.25	0.96	3.11 +/− 0.32	20	n.s
	2.5	1.92	2.29 +/− 0.22	41	0.01
	5	3.84	1.71 +/− 0.24	56	0.01
	10	7.69	1.26 +/− 0.19	67	0.01
	20	15.38	1.20 +/− 0.13	69	0.01

TABLE III-continued

PRODUCT	DOSE mg/Kg P.O admin.	QUANTITY of base	WEIGHT of thrombi*	VARIATION %	P**
Controls			3.78 +/- 0.36		
SR 25990E	10	3.84	1.48 +/- 0.15	60	0.001
	20	7.69	1.18 +/- 0.15	68	0.001

* = weight of thrombi in mg +/- standard error of the mean
P = U test of Kruskal - Wallis

For the toxicological study, the compounds were administered by the oral route in the form of a suspension in the same volume of water made up to 10% (wt/v) with gum arabic to groups of 10 fasted female rats of the Sprague Dawley strain weighing 120 to 135 grams.

The number of dead animals was determined 14 days after the administration of the compound under study. The lethal doses thus determined, expressed in weight of the salt administered, are presented in Table IV; these results show on the one hand that the toxicity of the racemic mixture is similar to that of the levo-rotatory isomer whereas the dextro-rotatory isomer is markedly less toxic, and, on the other hand, that the toxicity depends on the nature of the acid used to form the salt.

TABLE IV

PRODUCTS	D 10	D 50 ( )	D 90	ABSOLUTE LETHAL DOSE
PCR 4099 (racemate)	1318	1615 (1448-1747)	1979	2000
SR 25989 A	1259	1702 (1443-1797)	2299	2000
SR 25990 A	3055	4316 (3569-5705)	6137	5000
SR 25990 C	2257	2591 (2372-2805)	2974	4000
SR 25990 D	2634	4268 (3581-6012)	6914	5000

( ) = confidence interval

The pharmacological study just presented has demonstrated the interesting inhibitory properties towards platelet aggregation of the compound Id and the absence of any activity of its isomer I1.

The medicine of the invention can be made available for oral administration in the form of tablets, sugar-coated tablets, capsules, drops, granules or a syrup. It can also be made available for rectal administration in the form of suppositories or for parenteral administration in the form of an injectable solution.

Each unit dose contains advantageously from 0.001 g to 0.100 g of the derivative of the invention, and the daily doses to be administered may vary from 0.001 g to 0.500 g of active ingredient depending on the age of the patient and the severity of the disorder to be treated. Some pharmaceutical formulations of the medicine of the invention will be given below as non-restrictive examples.

(1) Tablets
Active ingredient: 0.010 g
Excipient: lactose, powdered sugar, rice-starch, alginic acid, magnesium stearate

(2) Sugar-coated tablets
Active ingredient: 0.005 g
Excipient: magnesium stearate, maize starch, gum arabic, shellac, white sugar, glucose, white wax, carnauba wax, paraffin, cochineal.

(3) Capsules
Active ingredient: 0.025 g
Excipient: magnesium stearate, maize starch, lactose.

(4) Injectable solution
Active ingredient: 0.050 g
Isotonic saline q.s.p. 3 ml.

(5) Suppositories
Active ingredient: 0.030 g
Semi-synthetic triglycerides q.s.p. 1 suppository.

On account of its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracoporeal blood circuits or the consequence of complications in atheroma.

We claim:

1. Dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer and its pharmaceutically acceptable salts.

2. Hydrochloride of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

4. Hydrobromide of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

5. Taurocholate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

6. Pharmaceutical composition which comprises an effective platelet aggregation inhibiting amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

7. Composition according to claim 6, comprising unit doses containing from 0.001 g to 0.100 g of active ingredient.

* * * * *

Exhibit B

US006429210B1

(12) **United States Patent**
Bousquet et al.

(10) **Patent No.: US 6,429,210 B1**
(45) **Date of Patent: Aug. 6, 2002**

(54) **POLYMORPHIC CLOPIDOGREL HYDROGENESULPHATE FORM**

(75) Inventors: **André Bousquet**, Sisteron; **Bertrand Castro**, Kremlin-Bicêtre; **Jean Saint-Germain**, Sisteron, all of (FR)

(73) Assignee: **Sanofi-Synthelabo**, Paris (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/623,333**

(22) PCT Filed: **Jun. 10, 1999**

(86) PCT No.: **PCT/FR99/01371**

§ 371 (c)(1),
(2), (4) Date: **Apr. 5, 2001**

(87) PCT Pub. No.: **WO99/65915**

PCT Pub. Date: **Dec. 23, 1999**

(30) **Foreign Application Priority Data**

Jun. 15, 1998 (FR) 98 07464

(51) **Int. Cl.**^{7} **A61K 31/4365**; C07D 495/04
(52) **U.S. Cl.** **514/301**; 546/114
(58) **Field of Search** 546/114; 514/301

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Primary Examiner—Charanjit S. Aulakh
(74) *Attorney, Agent, or Firm*—Paul E. Dupont; Michael D. Alexander

(57) **ABSTRACT**

Novel orthorombic polymorph of clopidogrel hydrogen sulfate or hydrogen sulfate of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-acetate and a process for its preparation.

15 Claims, 7 Drawing Sheets

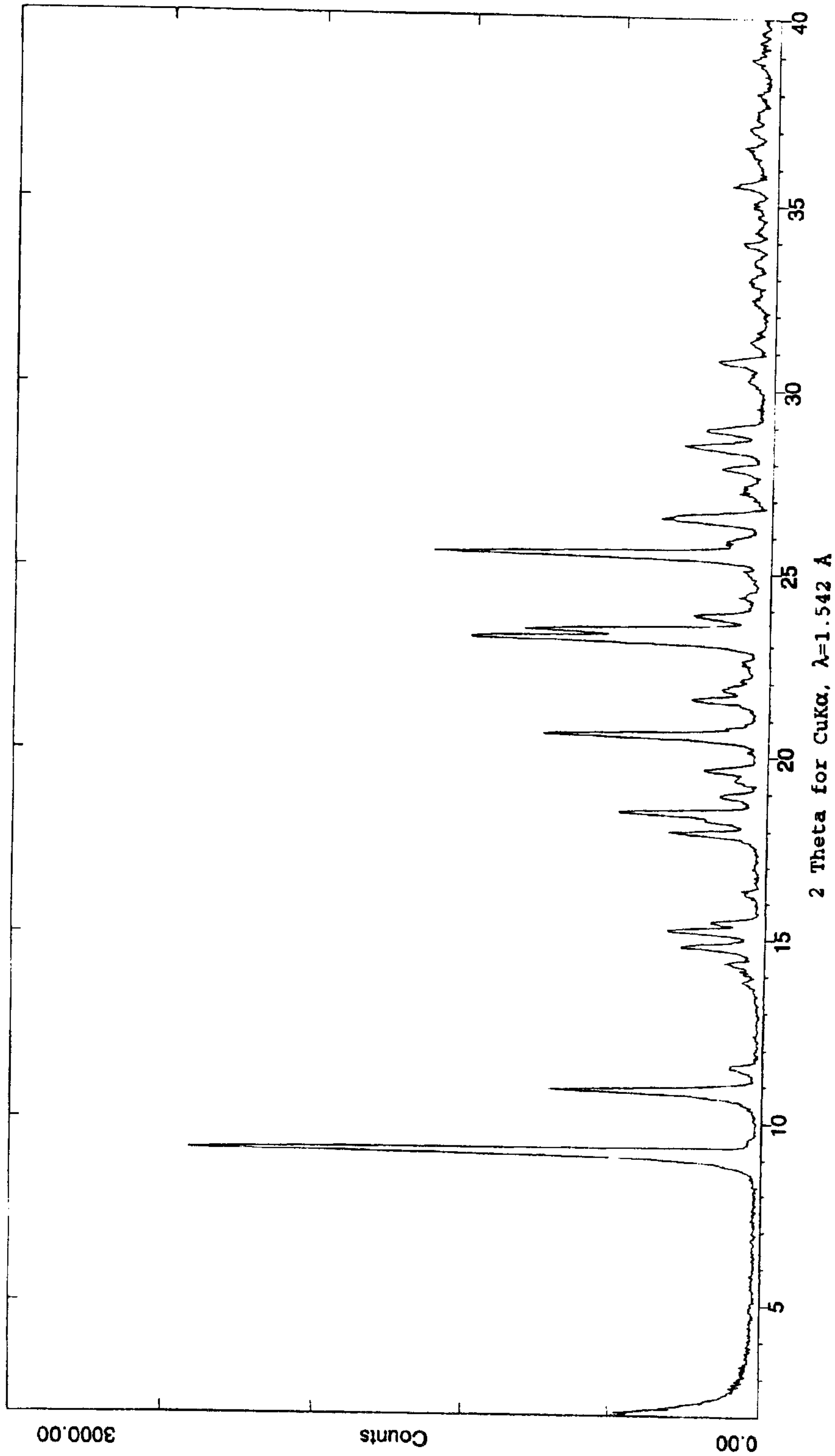


FIGURE 1

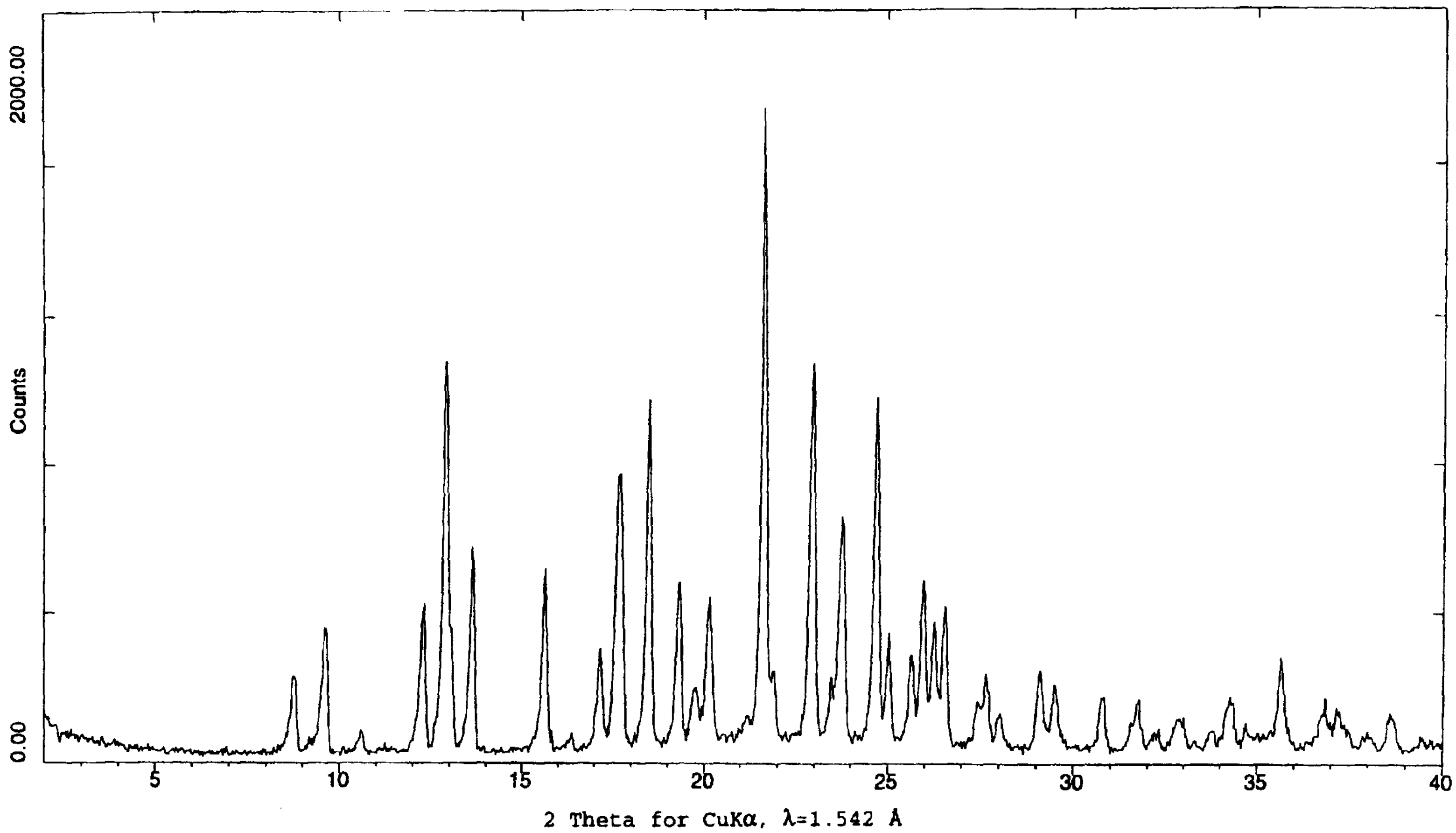
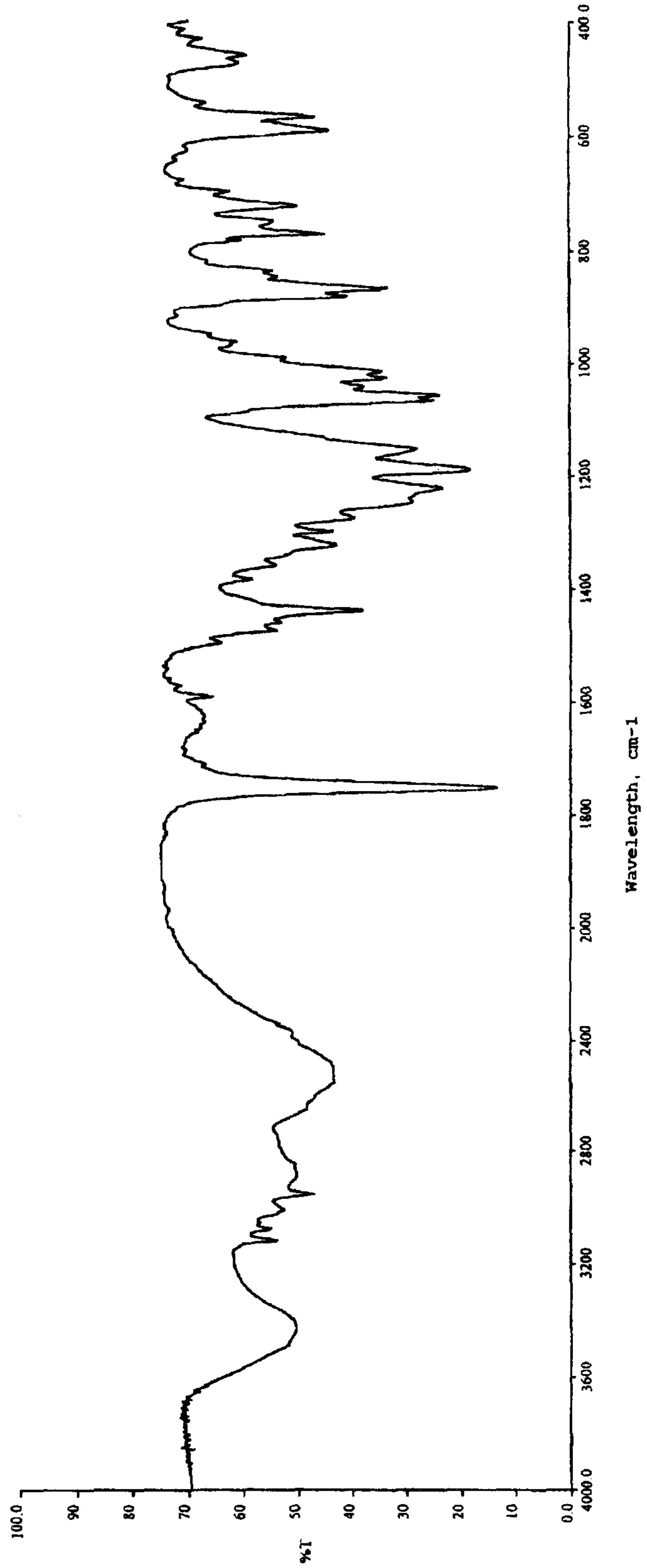


FIGURE 2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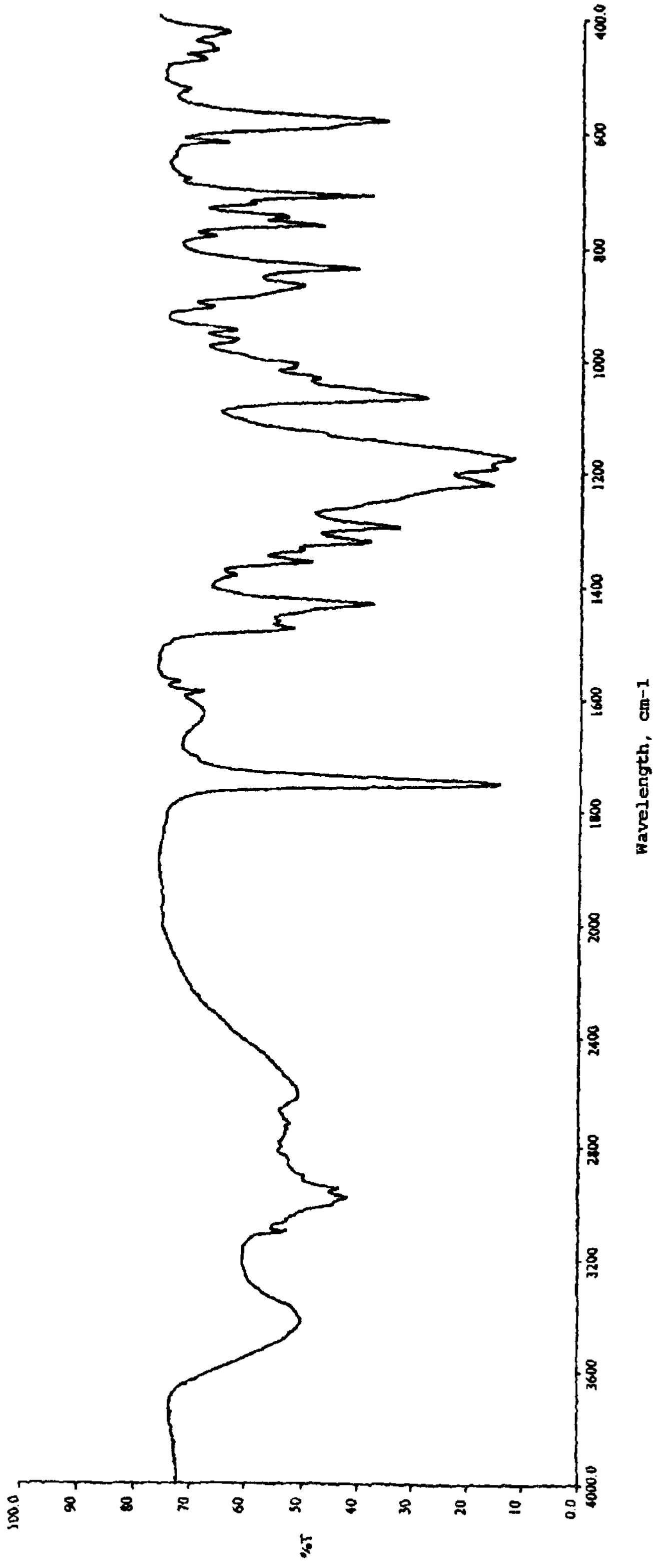
400.0
Wavelength, cm-1

FIGURE 3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400.0
Wavelength, cm-1

FIGURE 4

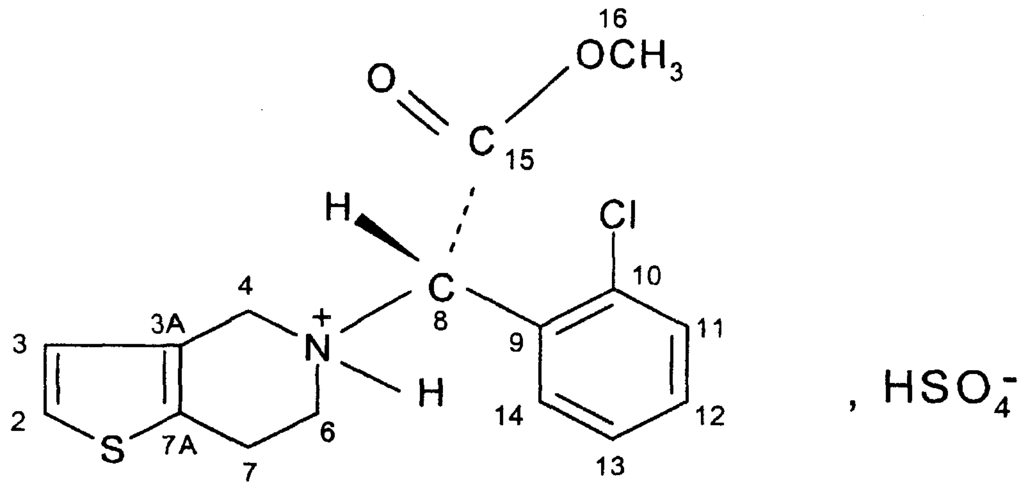
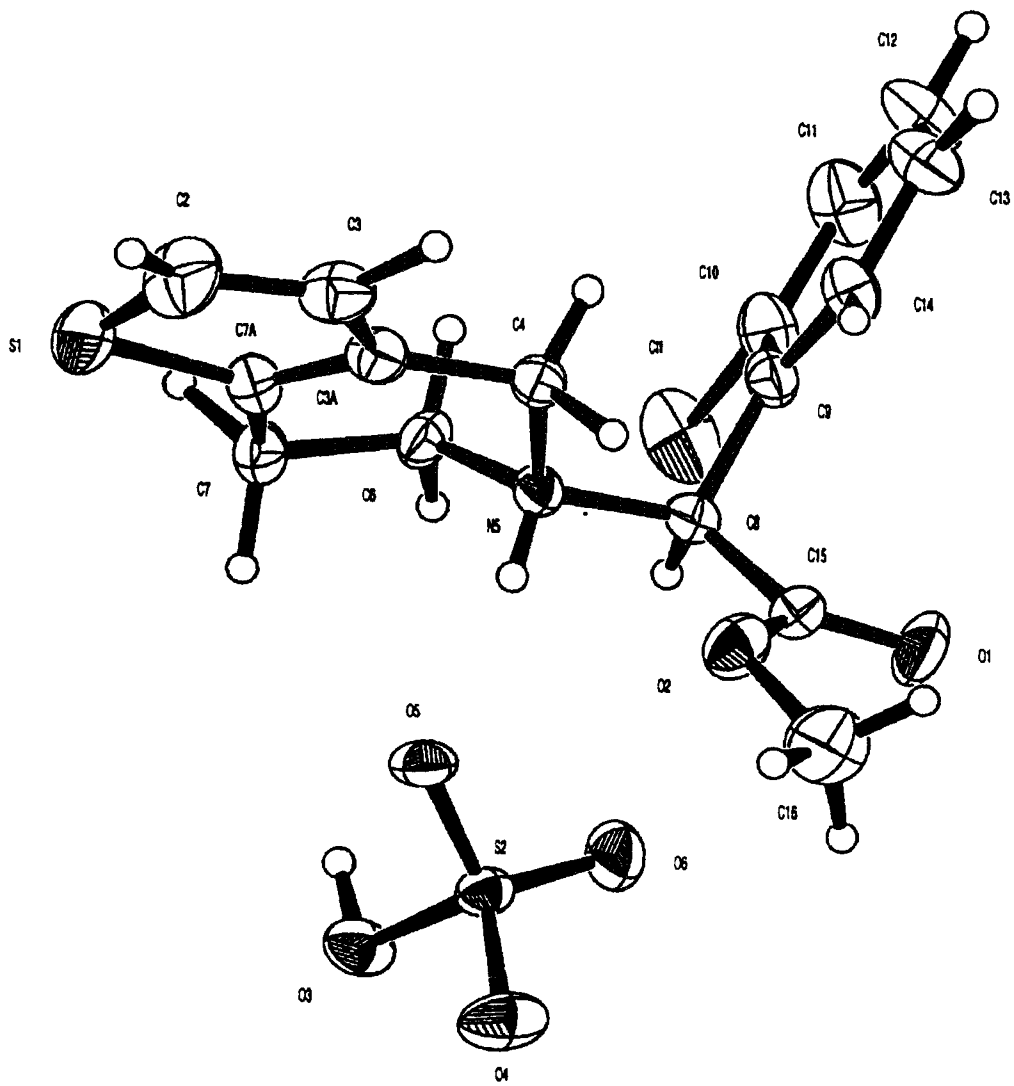


FIGURE 5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C2
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C14
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O6
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O4

FIGURE 6

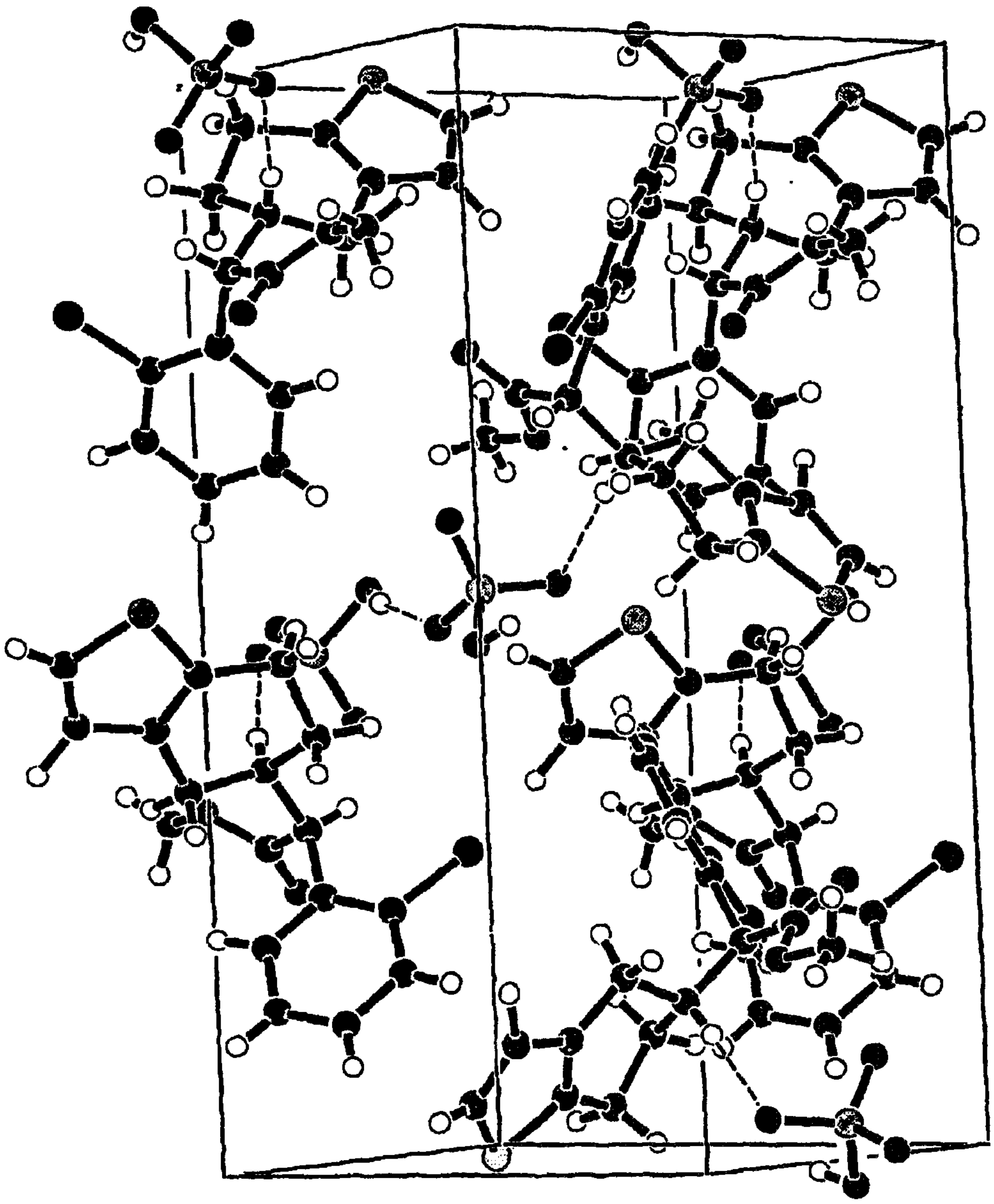

FIGURE 7

POLYMORPHIC CLOPIDOGREL HYDROGENESULPHATE FORM

The present invention relates to a novel polymorph of clopidogrel hydrogen sulfate or the hydrogen sulfate of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridine-5-acetate and a process for its preparation. More particularly, the invention relates to the preparation of this polymorph called Form 2 and to the isolation of this compound in this novel crystalline form, as well as to pharmaceutical compositions containing it.

Clopidogrel hydrogen sulfate is a platelet aggregation inhibitor which was described for the first time in EP 281459. The synthetic process claimed in this patent leads to the preparation of clopidogrel hydrogen sulfate which is called Form 1. It has now been discovered that clopidogrel hydrogen sulfate can exist in different polymorphic crystalline forms which differ from each other by their stability, their physical properties, their spectral characteristics and the process for their preparation.

Thus, one of these novel polymorphic forms is the object of the present invention, it is described in the present application and will be named Form 2.

The present invention also relates to a process for the preparation of clopidogrel hydrogen sulfate in its polymorphic Form 2.

Patent EP 281459 describes enantiomers of tetrahydrothienopyridine derivatives and their pharmaceutically acceptable salts. EP 281459 specifically claims clopidogrel hydrogen sulfate, i.e. the dextrorotatory isomer which possesses an excellent platelet aggregation inhibiting activity whereas the levorotatory isomer is less active and less well tolerated. Patent EP 281459, filed ten years ago, makes no reference to the existence of specific polymorphic forms of clopidogrel hydrogen sulfate. The synthesis described in EP 281459 leads to the preparation of the hydrogen sulfate of the polymorph of clopidogrel Form 1. Nor does EP 281459 suggest the existence of different polymorphic forms of clopidogrel or of clopidogrel hydrogen sulfate.

According to all of the teachings of the above documents, the dextrorotatory isomer of clopidogrel is prepared by salt formation from the racemic compound using an optically active acid such as 10-L-camphorsulfonic acid in acetone, followed by successive recrystallisations of the salt until a product with constant rotatory power was obtained, followed by release of the dextrorotatory isomer from its salt by a base. Clopidogrel hydrogen sulfate is then obtained in a standard manner by the dissolution of said base in acetone cooled in ice and addition of concentrated sulfuric acid to precipitation. The precipitate thus obtained is then isolated by filtration, washed and dried to give clopidogrel hydrogen sulfate in the form of white crystals whose melting point is 184° C. and optical rotation +55.1° (c=1.891/CH_3OH).

The process described in the prior art leads only to the form 1 of clopidogrel hydrogen sulfate.

Thus, the present invention relates to the polymorphic form called Form 2 of clopidogrel hydrogen sulfate which, like Form 1 of this compound, is useful as a medicine for prophylaxis and the treatment of thrombosis by acting as a platelet aggregation inhibitor. As far as the use of clopidogrel and its salts is concerned, reference may be made to Drugs of the Future, 1993, 18, 2, 107–112. Polymorphic Form 2 of clopidogrel hydrogen sulfate is thus used as active ingredient for the preparation of a medicine, in combination with at least one pharmaceutically acceptable excipient, in the same indications as Form 1.

It has now been found that if clopidogrel hydrogen sulfate is crystallised from a solvent, either the crystalline form, Form 1, corresponding to that of the product obtained according EP 281459 mentioned above may be produced or a new, very stable crystalline form having a well-defined structure designated Form 2 below. More particularly, it has been found that the novel crystalline form of clopidogrel hydrogen sulfate, Form 2, is at least as stable as the Form 1 described and that it does not convert spontaneously into the previously known Form 1. Furthermore, Form 2 bulk solid is more compact and much less electrostatic than Form 1 and may hence be more readily subjected to any treatment under the usual conditions of pharmaceutical technology and, in particular, of formulation on an industrial scale.

It has moreover been observed that Form 2 exhibits a lower solubility than Form 1 as a result of its greater thermodynamic stability.

The difference between the new crystalline form of clopidogrel hydrogen sulfate according to the present invention, Form 2, and Form 1 is apparent on examination of the FIGS. **1** to **4**, whereas the FIGS. **5** to **7** demonstrate the structure in the crystals of Form 2.

The FIGS. **1** to **7** are characterised as follows:

FIG. **1** gives the X-ray powder diffractogram of clopidogrel hydrogen sulfate Form 1;

FIG. **2** shows the X-ray powder diffractogram of clopidogrel hydrogen sulfate Form 2;

FIG. **3** shows the infrared spectrum of Form 2;

FIG. **4** shows the infrared spectrum of Form 1;

FIG. **5** shows the structural formula of clopidogrel hydrogen sulfate with the numbering of the atoms in the crystalline Form 2;

FIG. **6** shows the spatial conformation of Form 2 clopidogrel hydrogen sulfate;

FIG. **7** shows the stacking of the molecules of Form 2 clopidogrel hydrogen sulfate in the unit cell of the crystal.

It was observed from the crystallographic data that the crystalline structure of Form 1 contains two crystallographically independent cations of clopidogrel and two independent bisulfate anions. The two independent cations are of similar conformation.

The crystallographic data of Form 2 show that it contains one crystallographically independent clopidogrel cation-bisulfate anion pair.

In the two forms, the cations are protonated axially and the nitrogen atom has the R configuration; the conformation of the cations in Form 2 is different from that observed in Form 1.

No site is occupied by solvent molecules in the molecular arrangement of the two crystalline forms.

The arrangement of the anions is very different in the two crystalline structures. The crystalline structure of Form 2 (orthorhombic) is less dense (1.462 g/cm^3) than the crystalline structure (monoclinic) of Form 1 (1.505 g/cm^3).

According to another feature, the object of the present invention is a process for the preparation of Form 2 of clopidogrel hydrogen sulfate wherein:

(a) methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-acetate camphorsulfonate is suspended in an organic solvent,

(b) the camphorsulfonic acid is extracted with an aqueous alkaline solution of potassium carbonate and the organic phase is washed with water,

(c) the organic phase is concentrated in a vacuum and the concentrated residue is taken up in acetone,

(d) 80% sulfuric acid is added,

(e) the mixture is heated to reflux, the product crystallises, the mixture is cooled, filtered and the crystals are

washed, then dried under reduced pressure to give clopidogrel hydrogen sulfate Form 1,

(f) the resulting mother liquors, yield after a 3 to 6 months period crystals of clopidogrel hydrogen sulfate Form 2.

Furthermore, the invention concerns a process for the preparation of (+)-(S) clopidogrel hydrogen sulfate Form 2 wherein:

the resulting mother liquors of crystallisation of Form 1 of (+)-(S) clopidogrel hydrogen sulfate yield after a 3 to 6 months period crystals of clopidogrel hydrogen sulfate Form 2.

The resulting hydroacetonic mother liquors of crystallisation of Form 1 of (+)-(S) clopidogrel hydrogen sulfate contains from 0.3 to 1% of water.

Those mother liquors contains until more or less 10% of clopidogrel hydrogen sulfate, this amount being calculated on the bases of the ammount of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-acetate camphorsulfonate used for the transformation into hydrogen sulfate.

The mother liquors yield slowly after a 3 to 6 months period, at a temperature below 40° C., clopidogrel hydrogen sulfate Form 2.

According to another of its features, the present invention relates to another process for the preparation of Form 2 of clopidogrel hydrogen sulfate wherein;

(a) methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-acetate camphorsulfonate is suspended in an organic solvent,

(b) the camphorsulfonic acid is extracted with an aqueous alkaline solution of potassium carbonate and the organic phase is washed with water,

(c) the organic phase is concentrated in a vacuum and the concentrated residue is taken up in acetone,

(d) 96% sulfuric acid is added at 20° C. and the solution is seeded with clopidogrel hydrogen sulfate Form 2,

(e) the product crystallises, the mixture is cooled, filtered and the crystals are washed, then dried under reduced pressure to give clopidogrel hydrogen sulfate Form 2.

Another alternative consists of subjecting the crystalline suspension to mechanical shearing with the aid of a shearing device. This device may attain a speed of rotation of about 10,000 to 15,000 revolutions per minute. Devices equipped with these characteristics are, for example, of the Turrax® type sold by IKA-Werke (DE).

Furthermore, these devices are suited to the treatment of industrial quantities.

The principe is to obtain by crushing small particules out of a solution which only contains a part of the sulfuric acid. The remaining part of acid will then be added slowly to allow crystal growth. Experiments proceeded starting with the addition of 10% of the amount of the necessary sulfuric acid.

Thus, the object of the present invention is Form 2 of clopidogrel hydrogen sulfate characterised by the X-ray powder diffraction profile given in TABLE I.

More particularly, Form 2 is also characterised by a melting point of 176° C., determined by differential enthalpic analysis (DSC) and by characteristic absorptions in the infrared and in the near infrared.

Some physical properties and the behaviour of the novel crystalline form of clopidogrel hydrogen sulfate according to the invention are completely different from those of Form 1 as was demonstrated by examining the two forms according to standard methods and procedures.

The X-ray powder diffraction profile (angle of diffraction) was determined with a Siemens D500TT diffractometer. The characteristic powder diffractograms between 2 and 40° in 2θ (2 theta, deg., for CuKα, λ=1.542 Å) Bragg angles are shown in FIG. 1 for Form 1 and in FIG. 2 for Form 2. The significant reflections of FIG. 1 are recorded in TABLE II whereas those of FIG. 2 are collected in TABLE I. In TABLES I and II, d is the interlattice distance and I/I_o represents the relative intensity, expressed as a percentage of the most intense reflection.

TABLE I

Form 2
Significant reflections shown in FIG. 2

d (Å)	I/I_0
4.11	100.0
6.86	61.7
3.87	61.4
3.60	56.3
4.80	55.8
5.01	44.4
3.74	37.9
6.49	33.1
5.66	29.8

TABLE II

Form 1
Significant reflections shown in FIG. 1

d (Å)	I/I_0
9.60	100.0
3.49	58.8
3.83	52.0
3.80	42.5
4.31	39.0
8.13	37.2
4.80	25.5
3.86	19.1
5.80	16.8
4.95	16.8

The differential enthalpy analysis (DSC) of the Forms 1 and 2 was carried out comparatively using a Perkin Elmer apparatus DSC7, calibrated by reference to indium. For the calorimetric analysis 2.899 mg of Form 1 or 2.574 mg of Form 2 were used, as obtained in EXAMPLE 2, in a crimped and pierced aluminium cup in a temperature range from 40° to 230° C. with a rate of heating of 10° C./minute. The melting point and the enthalpy of fusion are indicated in TABLE III. The melting point corresponds to the characteristic melting temperature obtained by DSC. This value may also be defined as being the temperature corresponding to the intersection between the baseline and the tangent to the melting peak curves observed by DSC.

TABLE III

Melting point and enthalpy

	Form 1	Form 2
Melting point (° C.)	181.2	176.0
Enthalpy of fusion (J/g)	77	87

The difference between the new Form 2 and Form 1 of clopidogrel hydrogen sulfate has also been demonstrated by infrared spectroscopy. The Fourier transform (FTIR) IR spectra were obtained with a Perkin Elmer system 2000 spectrometer with a resolution of 4 cm^{-1} from 4000 cm^{-1} to 400 cm^{-1}. The samples of Form 1 or Form 2 are prepared in

the form of 0.3% KBr disks. The disks were subjected to a compression of 10 tons for 2 minutes. Each sample was examined after 4 accumulated scans.

The comparison of characteristic bands in terms of wavelength (in cm^{-1}) and intensity (as percentage of transmittance) is illustrated in TABLE IV.

TABLE IV

Infrared Spectra			
Form 1		Form 2	
Wavelength (cm^{-1})	% transmittance	Wavelength (cm^{-1})	% transmittance
2987	42	2551	43
1753	14	1753	13.4
1222	16	1497	63,7
1175	12	1189	18
841	40	1029	33.2

TABLE IV shows that Form 2 exhibits characteristic absorptions at 2551 cm^{-1}, 1497 cm^{-1}, 1189 cm^{-1} and 1029 cm^{-1} which are absent from Form 1.

The particular structure of the crystals of Form 2 was elucidated by single-crystal X-ray diffraction analysis using a MSC-Rigaka AFC6S diffractometer and the software SHELXS-90 and SHELXS-93 at a SG IRIS Indigo work station. The position of the C-H hydrogens was generated at a distance of 0.95 Å. The crystallographic data, in particular the unit cells leghts (a, b, c), the angles (α, β, γ) and the volume of each unit cell are shown in TABLE V.

TABLE V

Crystallographic data and establishment of the structure of Form 2	
Crystalline system space group	Orthorhombic $P2_12_12_1$
Dimensions of unit cell:	
a	10.321(6) Å
b	20.118(9) Å
c	9.187(7) Å
α	90 degrees
β	90 degrees
γ	90 degrees
volume	1908(2) $Å^3$
Z	4
density (calculated)	1.462 g/cm^3
collected reflexions	2134
R factor	0.0473

The atomic coordinates of Form 2 are given in TABLE VI, the bond lengths in TABLE VII, the bond angles in TABLE VIII and the characteristics torsion angles in TABLE IX.

TABLE VI

atom	x	y	z	U(eq)
Cl(1)	0.2223(3)	0.21728(12)	0.4295(3)	0.0835(8)
S(1)	0.8085(2)	−0.00068(11)	0.3557(3)	0.0724(7)
S(2)	0.2840(2)	0.01908(8)	0.0013(2)	0.0412(4)
O(1)	0.3030(7)	0.2376(3)	−0.0528(7)	0.087(2)
O(2)	0.4630(6)	0.1637(3)	−0.0860(6)	0.060(2)
O(3)	0.2175(6)	−0.0350(3)	0.0957(6)	0.0551(14)
O(4)	0.2728(6)	−0.0093(3)	−0.1432(5)	0.074(2)
O(5)	0.4174(4)	0.0241(2)	0.0497(6)	0.0503(13)
O(6)	0.2146(5)	0.0800(2)	0.0199(7)	0.065(2)

TABLE VI-continued

atom	x	y	z	U(eq)
N(5)	0.4936(6)	0.1343(3)	0.1946(7)	0.0380(14)
C(2)	0.9111(10)	0.0427(5)	0.2500(13)	0.081(3)
C(3A)	0.7214(7)	0.1002(3)	0.2215(9)	0.047(2)
C(3)	0.8554(8)	0.0950(5)	0.1824(11)	0.060(2)
C(4)	0.6332(7)	0.1548(4)	0.1706(10)	0.044(2)
C(6)	0.4750(8)	0.1100(4)	0.3487(9)	0.045(2)
C(7)	0.5487(8)	0.0450(4)	0.3722(10)	0.051(2)
C(7A)	0.6833(8)	0.0526(3)	0.3144(9)	0.050(2)
C(8)	0.3940(8)	0.1880(4)	0.1574(9)	0.043(2)
C(9)	0.4119(7)	0.2523(3)	0.2360(9)	0.044(2)
C(10)	0.3435(8)	0.2688(4)	0.3613(10)	0.057(2)
C(11)	0.3630(10)	0.3292(4)	0.4290(11)	0.076(3)
C(12)	0.4545(10)	0.3734(4)	0.3773(12)	0.080(3)
C(13)	0.5223(10)	0.3579(4)	0.2550(12)	0.067(3)
C(14)	0.5019(8)	0.2980(3)	0.1863(10)	0.052(2)
C(15)	0.3823(8)	0.1995(4)	−0.0079(11)	0.053(2)
C(16)	0.4462(16)	0.1687(6)	−0.2422(11)	0.096(4)

TABLE VII

atom	atom	distance
Cl(1)	C(10)	1.742(8)
S(1)	C(2)	1.682(12)
S(1)	C(7A)	1.722(8)
S(2)	O(6)	1.429(5)
S(2)	O(4)	1.450(5)
S(2)	O(5)	1.450(5)
S(2)	O(3)	1.551(5)
O(1)	C(15)	1.195(9)
O(2)	C(15)	1.314(10)
O(2)	C(16)	1.448(10)
N(5)	C(6)	1.510(10)
N(5)	C(4)	1.515(9)
N(5)	C(8)	1.530(9)
C(2)	C(3)	1.350(13)
C(3A)	C(7A)	1.341(10)
C(3A)	C(3)	1.432(10)
C(3A)	C(4)	1.501(10)
C(6)	C(7)	1.528(10)
C(7)	C(7A)	1.495(11)
C(8)	C(9)	1.493(10)
C(8)	C(15)	1.541(12)
C(9)	C(14)	1.384(10)
C(9)	C(10)	1.390(11)
C(10)	C(11)	1.379(11)
C(11)	C(12)	1.382(12)
C(12)	C(13)	1.359(13)
C(13)	C(14)	1.378(11)

The distances are in Angstroms. The standard deviations estimated on the last place of decimals are given in parentheses.

TABLE VIII

atom	atom	atom	angle
C(2)	S(1)	C(7A)	91.2(4)
O(6)	S(2)	O(4)	114.0(4)
O(6)	S(2)	O(5)	112.3(3)
O(4)	S(2)	O(5)	112.6(3)
O(6)	S(2)	O(3)	108.2(3)
O(4)	S(2)	O(3)	101.6(3)
O(5)	S(2)	O(3)	107.3(3)
C(15)	O(2)	C(16)	115.3(9)

TABLE VIII-continued

The intramolecular bond angles between non-hydrogen atoms

atom	atom	atom	angle
C(6)	N(5)	C(4)	110.1(6)
C(6)	N(5)	C(8)	110.6(6)
C(4)	N(5)	C(8)	114.5(5)
C(3)	C(2)	S(1)	113.7(7)
C(7A)	C(3A)	C(3)	113.0(8)
C(7A)	C(3A)	C(4)	122.8(7)
C(3)	C(3A)	C(4)	124.1(8)
C(2)	C(3)	C(3A)	110.7(9)
C(3A)	C(4)	N(5)	109.5(6)
N(5)	C(6)	C(7)	110.2(7)
C(7A)	C(7)	C(6)	108.9(6)
C(3A)	C(7A)	C(7)	124.9(7)
C(3A)	C(7A)	S(1)	111.4(6)
C(7)	C(7A)	S(1)	123.7(6)
C(9)	C(8)	N(5)	114.9(6)
C(9)	C(8)	C(15)	110.9(6)
N(5)	C(8)	C(15)	112.2(7)
C(14)	C(9)	C(10)	117.1(7)
C(14)	C(9)	C(8)	119.9(8)
C(10)	C(9)	C(8)	123.0(7)
C(11)	C(10)	C(9)	120.7(8)
C(11)	C(10)	Cl(1)	117.8(7)
C(9)	C(10)	Cl(1)	121.4(6)
C(10)	C(11)	C(12)	120.7(9)
C(13)	C(12)	C(11)	119.3(9)
C(12)	C(13)	C(14)	120.0(9)
C(13)	C(14)	C(9)	122.2(9)
O(1)	C(15)	O(2)	126.7(9)
O(1)	C(15)	C(8)	119.3(9)
O(2)	C(15)	C(8)	114.0(7)

The angles are in degrees. The standard deviations estimated on the last place of decimals are given in parentheses.

TABLE IX

Conformation and characteristic torsion angles

(1)	(2)	(3)	(4)	angle
C(7A)	S(1)	C(2)	C(3)	−1.1(9)
S(1)	C(2)	C(3)	C(3A)	0.9(12)
C(7A)	C(3A)	C(3)	C(2)	0.0(12)
C(4)	C(3A)	C(3)	C(2)	177.1(8)
C(7A)	C(3A)	C(4)	N(5)	−19.7(11)
C(3)	C(3A)	C(4)	N(5)	163.4(8)
C(6)	N(5)	C(4)	C(3A)	50.2(8)
C(8)	N(5)	C(4)	C(3A)	175.7(7)
C(4)	N(5)	C(6)	C(7)	−67.3(8)
C(8)	N(5)	C(6)	C(7)	165.0(6)
N(5)	C(6)	C(7)	C(7A)	47.8(9)
C(3)	C(3A)	C(7A)	C(7)	−179.1(8)
C(4)	C(3A)	C(7A)	C(7)	3.8(13)
C(3)	C(3A)	C(7A)	S(1)	−0.8(9)
C(4)	C(3A)	C(7A)	S(1)	−177.9(6)
C(6)	C(7)	C(7A)	C(3A)	−17.6(12)
C(6)	C(7)	C(7A)	S(1)	164.3(6)
C(2)	S(1)	C(7A)	C(3A)	1.1(7)
C(2)	S(1)	C(7A)	C(7)	179.4(8)
C(6)	N(5)	C(8)	C(9)	68.9(8)
C(4)	N(5)	C(8)	C(9)	−56.3(10)
C(6)	N(5)	C(8)	C(15)	−163.2(6)
C(4)	N(5)	C(8)	C(15)	71.6(8)
N(5)	C(8)	C(9)	C(14)	81.4(9)
C(15)	C(8)	C(9)	C(14)	−47.2(10)
N(5)	C(8)	C(9)	C(10)	−97.3(9)
C(15)	C(8)	C(9)	C(10)	134.2(8)
C(14)	C(9)	C(10)	C(11)	1.9(12)
C(8)	C(9)	C(10)	C(11)	−179.4(8)
C(14)	C(9)	C(10)	Cl(1)	176.9(6)
C(8)	C(9)	C(10)	Cl(1)	−4.4(11)
C(9)	C(10)	C(11)	C(12)	−2.6(14)
Cl(1)	C(10)	C(11)	C(12)	−177.8(8)

TABLE IX-continued

Conformation and characteristic torsion angles

(1)	(2)	(3)	(4)	angle
C(10)	C(11)	C(12)	C(13)	3(2)
C(11)	C(12)	C(13)	C(14)	−2(2)
C(12)	C(13)	C(14)	C(9)	1.1(14)
C(10)	C(9)	C(14)	C(13)	−1.1(12)
C(8)	C(9)	C(14)	C(13)	−179.9(8)
C(16)	O(2)	C(15)	O(1)	−4.3(13)
C(16)	O(2)	C(15)	C(8)	174.5(8)
C(9)	C(8)	C(15)	O(1)	−54.0(10)
N(5)	C(8)	C(15)	O(1)	176.0(7)
C(9)	C(8)	C(15)	O(2)	127.1(7)
N(5)	C(8)	C(15)	O(2)	−2.8(9)

The angles are in degree. The standard deviations estimated on the last place of decimals are given in parentheses.

The sign is positive if, on looking from atom 2 to atom 3, atom 1 is superposed on atom 4 by a clockwise movement.

The crystallographic study with X rays, in particular the crystallographic data of TABLE I, the atomic coordinates of TABLE VI, the bond lengths of TABLE VII, the bond angles of TABLE VIII and the characteristic torsion angles of TABLE IX prove the structure proposed and illustrated in FIGS. **5** and **6**.

The Form 1 crystals are irregular plates and the crystals of Form 2 are agglomerates. Microscopic examination revealed that the crystals of the new Form 2 are morphologically different from those of Form 1.

As it is less electrostatic than Form 1 it is hence particularly suited to the manufacture of pharmaceutical compositions for the treatment of all diseases in which a platelet aggregation inhibitor is indicated.

Thus, according to another of its features, the object of the present invention is pharmaceutical compositions containing as active ingredient Form 2 of clopidogrel hydrogen sulfate characterised by the X ray powder diffraction profile illustrated in TABLE I.

Preferably, Form 2 of clopidogrel hydrogen sulfate according to the present invention is formulated in pharmaceutical compositions by the oral route containing 75 mg of active ingredient per dosage unit, in a mixture with at least one pharmaceutical excipient.

When a solid composition is prepared in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets may be coated with sucrose or other suitable materials or they may also be treated such that they have a prolonged or delayed activity and so that they continuously release a predefined quantity of active ingredient. A preparation of capsules is obtained by mixing the active ingredient with a diluant and by pouring the mixture obtained into soft or hard capsules.

The powders or granules dispersible in water may contain the active ingredient as a mixture with dispersion agents or wetting agents, or suspending agents like polyvinylpyrrolidone, likewise with sweetening agents or taste correctors. If it is desired to formulate the active ingredient for rectal administration, recourse is had to suppositories which are prepared with binders melting at the rectal temperature, for example cocoa butter or polyethyleneglycols.

For parenteral administration, aqueous suspensions, saline solutions or sterile and injectable solutions are used.

The active ingredient may also be formulated in the form of microcapsules, optionally with one or more supports or additives.

The following EXAMPLES illustrate the invention without in any way limiting it. Preparation of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine-5-acetate camphorsulfonate

400 kg of racemic methyl α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-acetate hydrochloride and 1840 kg of dichloromethane are loaded into a stirred reactor. Then 1200 kg of an 8% aqueous solution of sodium bicarbonate are added slowly. After decantation, the organic phase is concentrated in a vacuum. The concentrated residue is diluted with 1000 liters of acetone. A solution of 154 kg of 1 R-10 camphorsulfonic acid in 620 liters of acetone is added at 20–25° C. The mixture is cooled and methyl α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c] pyridine-5-acetate camphorsulfonate is crystallised by seeding if necessary. When crystallisation is abundant, the mixture is heated to reflux, then cooled to 25° C. The crystals are then filtered off and washed with acetone, then dried under reduced pressure. Thus, 196 kg of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-acetate camphorsulfonate are obtained, i.e. a yield of 33%. Preparation of Form 2 clopidogrel hydrogen sulfate

EXAMPLE 1A

50 g of clopidogrel camphorsulfate prepared as indicated above is introduced into a 250 ml reactor under nitrogen. Dichloromethane, 100 ml, is added and the mixture is stirred for 10 minutes. Then a solution of 9.1 g of potassium carbonate dissolved in 70 ml deionized water is introduced. The organic phase is separated and the aqueous phase is washed several times with dichloromethane. The organic phases are combined and concentrated in a vacuum. 229 ml of acetone is added to the concentrate and the solution is filtered through a 0.1μ to 0.22μ frit. The acetone solution containing the base is loaded into a reactor under nitrogen, and 7.4 g of an 80% sulfuric acid solution is added at 20° C., then the mixture is heated to reflux; crystallisation starts and reflux is maintained for 2 hours.

The solvent is distilled, the residue is cooled to a temperature of 0 to −5° C. and the crystals are filtered off on a Büchner funnel to obtain 21.4 g of Form 2 clopidogrel hydrogen sulfate after drying; m.p.=176±3° C.

EXAMPLE 1B

1200 kg of clopidogrel camphorsulfate prepared as indicated above is introduced into a 6000 l reactor under nitrogen. Dichloromethane, 2345 l, is added and the mixture is stirred for 30 minutes to 1 hour. Then a solution of 214.5 kg of potassium carbonate dissolved in 1827 l deionized water is introduced. The organic phase is separated and the aqueous phase is washed several times with dichloromethane. The organic phases are combined and concentrated in a vacuum. Acetone is added to the concentrate and the solution is filtered through a 0.1μ to 1μ filtration cartdridge. The acetone solution (3033 l) containing the base is loaded into a reactor under nitrogen, and 264.8 kg of an 80% sulfuric acid solution is added at 20° C.

The solvent is distilled, the residue is cooled to a temperature of 0 to −5° C. and the crystals are filtered off on a Büchner funnel to obtain 779.1 kg of Form 1 clopidogrel hydrogen sulfate after drying; m.p.=184±3° C.

The resulting mother liquors, at a temperature bellow 40° C., yield after a 3 to 6 months period crystals of clopidogrel hydrogen sulfate Form 2; m.p.=176±3° C.

EXAMPLE 1C

1200 kg of clopidogrel camphorsulfate prepared as indicated above is introduced into a 6000 l reactor under nitrogen. Dichloromethane, 2345 l, is added and the mixture is stirred for 30 minutes to 1 hour. Then a solution of 214.5 kg of potassium carbonate dissolved in 1827 l deionized water is introduced. The organic phase is separated and the aqueous phase is washed several times with dichloromethane. The organic phases are combined and concentrated in a vacuum. Acetone is added to the concentrate and the solution is filtered through a 0.1μ to 1μ filtration cartdridge. The acetone solution (3033 l) containing the base is loaded into a reactor under nitrogen, and 264.8 kg of an 96% sulfuric acid solution is added at 20° C.

The solvent is distilled, the residue is cooled to a temperature of 0 to −5° C. and the crystals are filtered off on a Büchner funnel to obtain 785.3 kg of Form 1 clopidogrel hydrogen sulfate after drying; m.p.=184±3° C.

The resulting mother liquors, at a temperature bellow 40° C., yield after a 3 to 6 months period crystals of clopidogrel hydrogen sulfate Form 2; m.p.=176±3° C.

EXAMPLE 2

Dichloromethane, 909 l, and 450 kg of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c] pyridine-5-acetate camphorsulfonate are loaded into a reactor. The camphorsulfonic acid is extracted by means of an aqueous solution of 80 kg of potassium carbonate in 680 l of water. The organic phase is then washed with water. The dichloromethane is concentrated and the concentrated residue is taken up in 1140 liters of acetone. Then, 100 kg of 96% sulfuric acid is added at 20° C. Seeding is performed with 0.3 kg of clopidogrel hydrogen sulfate Form 2 obtained in EXAMPLE 1B or 1C. Clopidogrel hydrogen sulfate crystallises. It is filtered off, washed with acetone and dried under reduced pressure. Clopidogrel hydrogen sulfate Form 2, 310 kg, is obtained, i.e. a yield of 90.9%; m.p.=176±3° C.

EXAMPLE 3

Dichloromethane, 909 l, and 450 kg of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c] pyridine-5-acetate camphorsulfonate are loaded into a reactor. The camphorsulfonic acid is extracted by means of an aqueous solution of 80 kg of potassium carbonate in 680 l of water. The organic phase is then washed with water. The dichloromethane is concentrated and the concentrated residue is taken up in 1296 liters of acetone.

The temperature is then stabilised at 20° C. and the Turrax® is set into action. 10% of the global amount of 94–96% sulfuric acid (8.3 kg) is then added in a few minutes. Then 0.012 kg of clopidogrel hydrogen sulfate Form 2 obtain according to examples 1B or 1C are used for seeding. Clopidogrel hydrogen sulfate Form 2 crystallises. The mixture is left for 45 minutes under the action of Turrax®. The 90% of sulfuric acid at 94–96% (74.6 kg) are then added within 2 hours while Turrax® is still acting. Turrax® is stopped 30 minutes after the acid addition. The mixture is then stirred for 30 minutes at 20° C., filtered, wash with acetone and dried under vacuo.

Then 310 kg of clopidogrel hydrogen sulfate Form 2 are obtained, yield 90.9%; F=176±3° C.

What is claimed is:

1. A crystalline polymorph of (+)-(S) clopidogrel hydrogen sulfate (Form 2), the X ray powder diffractogram of which shows characteristic peaks expressed as interplanar distance at approximately 4.11; 6.86; 3.60; 5.01; 3.74; 6.49 and 5.66 Å.

2. A crystalline polymorph of (+)-(S) clopidogrel hydrogen sulfate (Form 2), the infrared spectrum of which exhibits

characteristic absorptions expressed in cm^{-1} at 2551, 1497, 1189 and 1029, with respective transmittance percentages of approximately 43; 63.7; 18 and 33.2.

3. A crystalline polymorph of (+)-(S) clopidogrel hydrogen sulfate (Form 2) having a melting point of 176+/−3° C.

4. A crystalline polymorph of clopidogrel hydrogen sulfate (Form 2) exhibiting the X ray powder diffractogram of FIG. **2**.

5. A crystalline polymorph of clopidogrel hydrogen sulfate (Form 2) exhibiting the infrared spectrum of FIG. **3**.

6. A crystalline polymorph of clopidogrel hydrogen sulfate (Form 2) exhibiting the X ray powder diffractogram which shows characteristic peaks expressed as interplanar distance at approximately 4.11; 6.86; 3.60; 5.01; 3.74; 6.49 and 5.66 Å and an infrared spectrum which shows characteristic absorptions expressed in cm^{-1} at 2551, 1497, 1189 and 1029, with respective transmittance percentages of approximately 43, 63.7, 18 and 33.2.

7. A pharmaceutical composition comprising an effective amount of the polymorph Form 2 of clopidogrel hydrogen sulfate according to claim **1** in combination with at least one pharmaceutical excipient.

8. (+)-(S) Clopidogrel hydrogen sulfate, the x-ray powder diffraction pattern of which shows a characteristic peak, expressed in terms of interplanar distance, at approximately 4.11 Å.

9. (+)-(S) Clopidogrel hydrogen sulfate, the x-ray powder diffraction pattern of which shows a characteristic peak, expressed in terms of interplanar distance, at approximately 6.86 Å.

10. (+)-(S) Clopidogrel hydrogen sulfate, the x-ray powder diffraction pattern of which shows a characteristic peak, expressed in terms of interplanar distance, at approximately 3.60 Å.

11. (+)-(S) Clopidogrel hydrogen sulfate, the x-ray powder diffraction pattern of which shows a characteristic peak, expressed in terms of interplanar distance, at approximately 3.87 Å.

12. (+)-(S) Clopidogrel hydrogen sulfate according to claim **8** wherein the x-ray powder diffraction pattern further shows a characteristic peak at approximately 6.86 Å.

13. (+)-(S) Clopidogrel hydrogen sulfate according to claim **12** wherein the x-ray powder diffraction pattern further shows a characteristic peak at approximately 3.60 Å.

14. (+)-(S) Clopidogrel hydrogen sulfate according to claim **9** wherein the x-ray powder diffraction pattern further shows a characteristic peak at approximately 3.60 Å.

15. (+)-(S) Clopidogrel hydrogen sulfate having an enthalpy of fusion of 87 J/g.

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